PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 49324-193	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/CA2004/000506	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant CELATOR TECHNOLOGIES INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.02.2005	05.09.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000506

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-25	as originally filed
Claims, Numbers	
1-41	as originally filed
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27-29,34-41 regarding industrial applicability

because:

☒ the said international application, or the said claims Nos. 27-29,34-41 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-41
Industrial applicability (IA)	Yes:	Claims	1-26,30-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I
Basis of opinion

1) Although claims 1 and 21, directed to a product claim, have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, namely a composition, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and **places an undue burden** on others seeking to establish the extent of the protection.

Hence, claims 1 and 21 do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of a single claim in each category followed by dependent claims covering features which are merely optional (Rule 6.4 PCT). Applicant should take care however not to add subject-matter which extends beyond the content of the application (Art. 19/34 PCT).

Failure to do so or to give convincing argumentations might lead to the substantive examination of only the first independent claim and its apending claims.

This objection applies ot claims 28 and 29, both directed to a method of treatment claim.

2) Severe clarity objection

The applicant argued with the letter that February 1 2005, that present invention resides in the fact that the therapeutic agent and at least one drug resistance modulator **both** must be **stably** associated with delivery vehicles having a mean diameter in the range of 50-300 nm.

He argued that the "both [the active agent and the modulator] must be stably associated" is a feature that is **essential** to the invention.
However this is not clear what is meant by "stably". In the light of the said letter of reply, since the applicant argued that D1 (for example) does not anticipate present application because "there is no basis to conclude that the adriamycin was encapsulated" [with monensin, the modulator], it seems that with the notion of "stably" is meant "co-encapsulated".
Conversely according to present claims 23,28,29, present paragraphs [9], [14], [17], [18], it is **not necessary** that the active agent and the modulator are co-encapsulated. This is in contradiction with the teaching of the said letter of reply.
Therefore in the absence of convincing argumentation, the terms "stably" or "co-encapsulated" can not be recognized as a feature that is essential to the invention.

Furthermore the applicant should provide a clear definition of the notion of "stably" because it places an undue burden for the skilled people trying to delimit the scope of the invention.
Herewith should the applicant argues that the composition or the compound/vehicle-association of prior art is not stable, he is kindly requested to provide evidence of his allegation. The mere statement is not sufficient, he must provide comparative tests showing that the composition of present application is stable, whereas the compositions of prior is not.
Since prior art demonstrated that the compositions described inthere are efficient for the treatment of drug resistance, it is thus implicit and a prerequisite that the compositions of prior art are stable.

If the applicant is able to show, e.g. by appropriate comparison tests, that differences do exist with respect to the parameters, it is questionnable whether the independent claims disclose all the features essential to manufacture products having parameters specified in the claims (Art. 5 and 6 PCT).

As it is not clear what is meant by "stably" (Art.6 PCT) , the present authority can not recognize it as a **characterizing distinguishing feature** that would confer novelty and inventive step to the subject-matter of present application. **Therefore the feature "both must be stably associated" will be ignored while assessing novelty and**

inventive step.

Consequently the objections regarding novelty and inventive step in § 2a-2d of the communication dated on August 10 2004 apply mutatis mutandis.

3) Results to be achieved (Art.6 PCT)

3a) To the objections of obscure terms, contradiction with the teaching of the description (see abobe §2), it should be added that the term "stably" does not delimit the scope of the protection to be sought and are rather to be construed as an attempt to define the invention by a **result to be achieved.**

Such definitions are only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, **such formulations are not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved by incorporating for example the type and amount of ingredients,...**

Hence applicant's attention is drawn with the fact such formulations **are not recognized as a technical feature** that can confer novelty to the application, **but as a result to be achieved and therefore will be ignored while assessing novelty.**

3b) The above objection applies to claims 30-41 with the formulations "**wherein said non-antagonistic effect exhibited...**" which are rather to be construed as an attempt to define the invention by a **result to be achieved.**

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

4) Claims 27-29,34-41 relate to subject-matter considered by this Authority to be covered by the -provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D14; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

6) Novelty and inventive step according to Art. 33(2) and 33(3) PCT

6a) The subject-matter of present application is nor novel nor inventive because D1, D2 and D14 (for the relevant passage see ISR) describe a composition for the treatment of multi drug resistance (MDR) containing a therapeutic agent and at least one drug resistance modulator characterized in that the said active substances are delivered by a vehicles having a mean diameter in the range of 50-300 nm.

It could be argued that prior art does not provide in a convincing manner that the compositons are stable. However since prior art demonstrated that the compositions described inthere are efficient for the treatment of drug resistance, it is thus implicit and a prerequisite that the compositions of prior art are stable, otherwise they would have not been efficient.

6b) The applicant alleges that present composition is efficient for the treatment of MDR. However he does not provide any evidence for the alleged effect, nor does he provide any evidence that "stably" is a feature essential to the invention. Therefore the problem is not solved and inventive step cannot be acknowledged.

Herewith it should be noted that the subject-matter of independent claims is so broadly claimed (no specific active substance, no specific modulator, no specific excipients) that it is difficult to believe that the problem can be solved over the whole scope. Therefore present application dos not fulfil the requirements of Art. 5 and 6 PCT for lack of support and disclosure.

6c) D3 (or D4 or D1-D2 or D14) describes a combination of an active substance and a drug resistance modulator.
The problem to be solved can be seen as providing a suitable carrier for delivering said active substances for the treatment of MDR.
D5-D13 teaches that when the active substances are transported by long-circulating nanosized particles such as lipoproteins, liposomes or nanoparticles, the MDR can be circumvented.

In view of this teaching, it is obvious for the skilled man in the art to use such vehicles in order to carry these active substances to the site of action.
Thus in the light of D3 (or D4 or D1-D2 or D14) combined with D5-D13 (or vice versa) the subject-matter of present application does not involve an inventive step.

Chou (see present application p.19 L.16-19) describes a method for setting up the **optimal ratio** therapeutic agent to drug resistance modulator for obtaining the desired non-anatagonistic, potentiating or synergistic effect.
As this method was made available to the public, this feature cannot be considered as a feature that will confer inventiveness to the present application because it seems that it consists **merely** in the combination of different features disclosed in prior art in order to obtain an optimal composition for the treatment of MDR. As this combination does not produce any non-obvious working inter-relationship inventive step cannot be acknowledged (see Guidelines CIV-Annex 2.1).

As long as the applicant does not provide a **surprising/synergetic** effect of the combined features (**which is not described in prior art**), inventive step cannot be acknowledged because present application would be considered as an **obvious association** of features **resulting in an obvious accumulation** of known effects (see Guidelines CIV-Annex 2.).

6d) Should the applicant renders the subject-matter of the present application novel by stressing out the relevance a technical feature that is not described explicitly in prior art or by introducing into the claims e.g. the use of a **specific carrier composition** or whatever, inventive step would be recognized **only if he demonstrates** that the

introduced technical feature provides **a surprising or synergetic effect** that the skilled man in the art **could not deduct from the prior art.**
In the absence of a surprising effect, inventive step cannot be acknowledged because the introduced technical feature would be considered as an **obvious alternative** that the skilled man in the art would perform **routinely** in order not to interact with prior art.

6e) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

Re Item VII
Certain defects in the international application

7) For the assessment of the present claims 27-29,34-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1-D2, D4 and D14 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

For the regional phase:

9) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the

content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

10) The applicant is kindly requested to **take account of the above objections and give convincing argumentations**. It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 6.3(b) (I), (ii) PCT (two part form claim). The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim **vis-à-vis** the state of the art and the significance thereof.